Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-33 and 35-42 are pending in the application, with claims 1 and 17 being the independent claims. The Examiner has withdrawn claims 3-7, 11-12, 15-16, 21-27, 30-33, 35, 37 and 42 from consideration.

Claims 1-2, 8, 13, 14, 17-20, 28, 36 and 38-41 have been rejected.

Claims 9, 10, and 29 are objected to, but the Examiner has indicated that they would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1, 2, 8, 13, 14, 17-20, 28, 36, and 38-41 under 35 U.S.C. § 103, as allegedly being unpatentable over Wu *et al.*, U.S. Patent No. 5,166,320 in view of Rossi *et al.*, U.S. Patent 5,144,019 and Hirsch *et al.*, U.S. Patent 5,428,132 (Paper No. 50, Page 2). Applicants respectfully disagree.

A. There is no motivation to combine the cited references; thus, an obviousness rejection cannot be maintained.

1. Wu et al. only indicate that the object of their invention was to provide an improved carrier system, but there is no indication that their object was met.

The Examiner has maintained that there is a motivation to combine the Wu *et al.* and Rossi *et al.* references. Specifically, the Examiner has stated:

> [T]he '320 patent specifically teaches that cell specificity is difficult in liposome based delivery systems, and that polycation-polynucleotide delivery systems overcome this specific liposome delivery problem.

(Paper No. 50, page 3.) (Citations omitted.) Again, Applicants respectfully disagree with the Examiner's characterization of the Wu *et al.* teachings.

Contrary to the Examiner's assertions, Wu *et al.* do *not* teach that their polycation-polynucleotide delivery systems overcome the "specific liposome delivery problem." Wu *et al.* only indicate that the "object" of the invention disclosed in their patent is to provide a "new and improved carrier system"; they do not teach that their polycation-protein conjugates are—in fact—new and improved over the other methods known in the art. An object of the invention is the goal that is to be achieved by the invention and there is no indication in Wu *et al.* that their stated objective, *inter alia*,"introduc[ing] foreign genes in a soluble non-toxic, cell specific manner into mammalian cells" was indeed achieved for all cell types and all therapeutic genes in all applications.

Nor is there any indication that their methods are improvements over liposome delivery methods. Again, Applicants emphasize that this is only the stated goal of the Wu *et al.* compositions. Specifically, Wu *et al.* provide no comparative data which demonstrates that their claimed methods and compositions are superior to other gene-delivery methods and in particular, they make no claims that their method is—in fact—superior to liposome-mediated delivery. They also make no claims that their gene-delivery method is superior for the targeted introduction of DNA into cells of the T-cell lineage. That the system works for select applications in hepatocytes is the full extent of the teaching in Wu *et al.* and their

statements that the system could be used for other mammalian cells is purely conjecture, for which they provide no support. Thus, it appears as though the Examiner is applying an impermissible "obvious to try" standard in order to improve upon liposome-mediated delivery. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

2. Assuming, arguendo, that the methods of Wu et al. were, in fact, improvements over liposome delivery methods, this does not make obvious the use of the Wu et al. methods for specific applications.

Assuming, *arguendo*, that the methods of Wu *et al.* were *generally* found to be superior to liposome methods for transfection of hepatocytes, that does not necessarily mean that the Wu *et al.* method is advantageous for *all* applications, in particular applications that target cells of the T cell lineage. As is known by those having ordinary skill in the art, the optimal methods of transfecting cells must be determined empirically on a case-by-case basis because each type of cell responds differently to the methods chosen, hence the multitude of methods and compounds utilized for gene transfer. "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). In the instant case, there is no particular teaching that the methods of Wu *et al.* would work for T cells.

3. There is no motivation to use targeted, cell specific transfection methods for the delivery of ribozymes to T cells as opposed to bulk, transfection methods.

Rossi *et al.*, according to the Examiner, teach ribozyme delivery to HIV-infected T cells using liposomes. Rossi *et al.* do suggest the use of calcium phosphate, lipofection, electroporation, and retroviral vectors as alternative methods to deliver the ribozyme (Column 6, line 65-67). Thus, the full extent of the teachings of Rossi *et al.* are limited to

nonspecific, bulk transfection methods, distinct from the targeted, cell-specific methods of the claimed invention. Specifically, Rossi *et al.* do not suggest that the introduction of ribozymes into cells may be possible in a *targeted, cell-specific* manner. If one wished to avoid the disadvantages of the liposomal system of Rossi *et al.*, one skilled in the art would be directed by the teachings of Rossi *et al.* itself, to the group listed in Rossi *et al.* rather than to use the transfection system of the claimed invention.

The use of liposomes as delivery vehicles, as in Rossi *et al.*, allows for the import of large quantities of the ribozyme of interest. In contrast, the quantity of ribozyme internalized by targeted cells using the specific protein-polycation conjugate of the claimed invention is limited by the quantity of receptors on the surface of the cell and the time it takes for the receptors to be internalized and recycled back to the cell surface and thereby can never exceed the levels of expression of a bulk transfection approach. As such, liposomes allow for a higher, albeit unspecific, degree of uptake into a variety of cells in contrast to the targeted approach of the claimed invention. Therefore, one skilled in the art, who would be attempting to use ribozymes to inhibit RNA transcription, would likely choose the alternate methods suggested by Rossi *et al.* or other bulk transfection protocols such as DEAE-Dextran, other cationic lipids, ballistic particle-DNA transfer, and glycerol or dimethyl sulfoxide shock treatments in conjunction with calcium phosphate-mediated transfection. A prior art reference must be considered in its entirety, i.e. as whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

4. Wu et al. disclose millions of compounds and the transfection methods preferentially relate to hepatocytes.

Wu *et al.* teach a gene delivery system comprising DNA complexes non-covalently bound to a ligand, conjugated to a foreign gene. The conjugate is formed by binding receptor-specific ligands, such as asialoglycoproteins, to polycations. At column 6, lines 1-14, Wu *et al.* state that glycoproteins, antibodies, or polypeptide hormones may be employed as ligands. As noted by the U.S. Court of Appeals for the Federal Circuit in *In re Baird,* 29 U.S.P.Q.2d 1550, 1552 (1994), a "disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a *preference* leading away from the claimed compounds." (Emphasis Added). The Examiner has previously asserted that Wu *et al.* "[d]iscloses only three types of targeting agents, glycoproteins, antibodies or polypeptide hormones . . . [t]his generic disclosure of three agents does not rise to the level of millions of possible components in which there is no direction to applicants claimed invention." (Paper No. 45, Page 3.) Applicants respectfully disagree.

The generic disclosure of glycoproteins, antibodies or polypeptide hormones in the Wu *et al.* patent cannot not be thought to comprise a small grouping of compounds. The disclosure of the use of "glycoproteins" as the targeting ligand suggests that *any* protein containing a sugar moiety can be used as the protein targeting ligand in the complex. The disclosure of "antibodies" comprises a group that includes, but is not limited to, immunoglobulin proteins and fragments which bind antigen (Fab fragments), as these latter molecules could also act in a similar fashion as immunoglobulins and retain many of the necessary characteristics of an antibody. Finally, the disclosure of "polypeptide hormones" can assert the use of *any* polypeptide hormone, *or any fragment thereof* which retains biological activity. Thus, contrary to the Examiner's suggestion, the disclosure of Wu *et*

al. encompasses thousands (and perhaps millions) of different combinations of protein-polycation-DNA conjugates.

Indeed, the success—if any—of the claimed methods of Wu *et al.* seem to be limited to gene delivery using asialoglycoproteins in hepatocytes. The specification, examples, and the claims of Wu *et al.* all point to solving the problem of hepatocyte transfection. In contradistinction, the claimed invention makes specific reference to targeting cells of the T cell lineage. In this respect, Applicants reiterate that the issue presented here is similar to the one presented in *In re Baird*, *supra*, where there was a disclosure of a vast number of possibilities and where the preferred examples are distinct from the claimed invention.

It is well known to those skilled in the art of immunology that cells of T cell lineage represent a *discrete* population of cells arising from hematopoietic stem cells located in the bone marrow. These bone marrow stem cells become immunocompetent cells of the T cell lineage within the thymus through a process of differentiation and maturation. Due to their specific function, cells of the T cell lineage contain a variety of surface markers or cluster determinants (CD) which are specific for these cells. Some of the CD molecules specific for T cells include: CD2, CD2R, CD3, CD4, CD7, CD8, CD25, CD30 CD45RA, CDw49b, CDw49d, CD57, CD69, CDw70, CD73, and CDw75 (Roitt, I., "The Activation of T-Cells," in Essential Immunology, Blackwell Scientific Publications, eds., London, (1991), pp.115-120). Due to the inherent specificity of T cells, it would not be obvious to one skilled in the art of immunology or even virology to combine the various references cited by the Examiner as Wu *et al.* is drawn to hepatocytes. The Wu *et al.* patent makes absolutely *no* mention of using their complexes for transfecting cells of T cell lineage.

B. At the time of filing, there would not have been a reasonable expectation of success.

1. At the time of filing, T cell cultures were difficult to maintain.

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Although methods to culture cells of the T cell lineage have vastly improved in recent years, at the time of filing, the culture of T cells was fraught with problems, let alone the many methods of manipulation. *See, e.g.,* Cohen *et al. Ciba Foundation Symposia 187*:179-193 (1994) (Exhibit A). Cohen *et al.* state that, "Difficulties maintaining fully functional CD4+ T cells in culture have historically limited the study of their role in tumour rejection as well as other clinical applications." The authors also state, "As the therapeutic value of current antitumour CD8+ T cell adoptive therapy becomes better defined, a strong impetus exists to determine optimal conditions for culturing CD4+ T cells." Thus, at the time of invention, it was difficult for those possessing ordinary skill in the art to minimally maintain functional T cells growing in culture. Furthermore, it is well known to those skilled in the art that the incorporation of foreign molecules into cells causes great stress on the transfected cells causing cell death from the transfection procedure alone, irrespective of the method chosen. Coupling the difficulty in *culturing* T cells, with the inherent mortality of cells undergoing transfection, would have been a notion with a low degree of success. Thus, at the time of the claimed invention, there would not have been a reasonable expectation of success.

2. It was known in the art that CD4 was down-regulated from cell surfaces in HIV-infected T cells.

In support of the assertion that there was an expectation of success in creating the claimed invention, the Examiner has stated that:

> [T]he '320 patent clearly teaches that 'It is known that most, if not all, mammalian cells possess cell surface binding sites or receptors that recognize, bind and internalize specific biological molecules, i.e. ligands. These molecules, once recognized and bound by the receptors, can be internalized within the target cells within membrane-limited vesicles via-receptor mediated endocytosis.'

(Paper No. 50, page 3.)

Again, the Examiner takes a general teaching in the art and asserts that it is applicable to specific applications. Just because "most" cells have surface binding sites that recognize and internalize specific molecules does not necessarily mean that targeting these sites is suitable for transfection of particular cell types with foreign nucleic acids. For example, certain cell surface binding sites may lead to vacuolization and degradation of the nucleic acid within lysozymes. In addition, depending on the state of the cell, certain receptors may be down-regulated resulting in a reduced number of receptors available for targeting. If the goal of transfection was introducing as much foreign DNA as possible to the target cell, one skilled in the art would likely avoid targeting these down-regulated receptors.

Indeed, at the time of filing, it was known in the art that HIV infection of T cells causes a loss of CD4 from cell surfaces via Nef, which acts by inducing CD4 endocytosis. *See* Aiken *et al.*, *Cell 76:* 853-64 (1994) (Exhibit B). Thus, one of ordinary skill in the art would recognize that the broad and general teachings of Wu *et al.* would not be completely applicable to all cell types and all cell surface targets, particularly in the transfection of HIV-infected T cells using CD4 as a target.

In view of the above, Applicants assert that, at the time of filing, there was no motivation to combine the cited references and that, at the time of filing, one of ordinary skill in the art would not have reasonably expected that the combination of references would be successful. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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